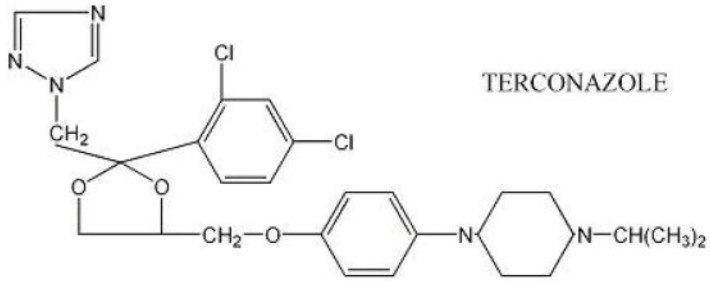
ZAZOLE - terconazole suppository
PharmaDerm

Rx only

DESCRIPTION

Zazole® Vaginal Suppositories (terconazole vaginal suppositories, 80 mg) are white to off-white suppositories for intravaginal administration containing 80 mg of the antifungal agent terconazole, *cis*-1-[p-[[2-(2,4-Dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-4-Isopropylpiperazine, in triglycerides derived from coconut and/or palm kernel oil (a base of hydrogenated vegetable oils) and butylated hydroxyanisole. The structural formula of terconazole is as follows:



Terconazole, a triazole derivative, is a white to almost white powder with a molecular weight of 532.47. It is insoluble in water; sparingly soluble in ethanol; and soluble in butanol.

CLINICAL PHARMACOLOGY

Following intravaginal administration of terconazole in humans, absorption ranged from 5-8% in three hysterectomized subjects and 12-16% in two non-hysterectomized subjects with tubal ligations.

Following oral (30 mg) administration of ^{14}C-labeled terconazole, the harmonic half-life of elimination from the blood for the parent terconazole was 6.9 hours (range 4.0-11.3). Terconazole is extensively metabolized; the plasma AUC for terconazole compared to the AUC for total radioactivity was 0.6%. Total radioactivity was eliminated from the blood with a harmonic half-life of 52.2 hours (range 44-60). Excretion of radioactivity was both by renal (32-56%) and fecal (47-52%) routes.
In vitro, terconazole is highly protein bound (94.9%) and the degree of binding is independent of drug concentration.
Photosensitivity reactions were observed in some normal volunteers following repeated dermal application of terconazole 2.0% and 0.8% creams under conditions of filtered artificial ultraviolet light.

Photosensitivity reactions have not been observed in U.S. and foreign clinical trials in patients who were treated with Zazole® Vaginal Suppositories.

Microbiology

Terconazole exhibits fungicidal activity *in vitro* against *Candida albicans*. Antifungal activity has also been demonstrated against other fungi. The MIC values of terconazole against most *Lactobacillus spp.* typically found in the human vagina were ≥128 mcg/mL; therefore these beneficial bacteria were not affected by drug treatment.
The exact pharmacologic mode of action of terconazole is uncertain; however, it may exert its antifungal activity by the disruption of normal fungal cell membrane permeability. No resistance to terconazole has developed during successive passages of *C. albicans*.

INDICATIONS AND USAGE

Zazole® Vaginal Suppositories are indicated for the local treatment of vulvovaginal candidiasis (monilasis). As Zazole® Vaginal Suppositories are effective only for vulvovaginitis caused by the genus Candida, the diagnosis should be confirmed by KOH smears and/or cultures.

CONTRAINDICATIONS

Patients known to be hypersensitive to terconazole or to any of the components of the suppositories.

WARNINGS

None.

PRECAUTIONS

General

Discontinue use and do not retreat with terconazole if sensitization, irritation, fever, chills, or flu-like symptoms are reported during use.
The base contained in the suppository formulation may interact with certain rubber or latex products, such as those used in vaginal contraceptive diaphragms, therefore concurrent use is not recommended.

Laboratory Tests
If there is lack of response to terconazole, appropriate microbiologic studies (standard KOH smear and/or cultures) should be repeated to confirm the diagnosis and rule out other pathogens.

Drug Interactions
The therapeutic effect of this product is not affected by oral contraceptive usage.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Studies to determine the carcinogenic potential of terconazole have not been performed.

Mutagenicity
Terconazole was not mutagenic when tested *in vitro* for induction of microbial point mutations (Ames test), or for inducing cellular transformation, or *in vivo* for chromosome breaks (micronucleus test) or dominant lethal mutations in mouse germ cells.

Impairment of Fertility
No impairment of fertility occurred when female rats were administered terconazole orally up to 40 mg/kg/day for a three month period.

Pregnancy

Teratogenic Effects: Pregnancy Category C;
There was no evidence of teratogencity when terconazole was administered orally up to 40 mg/kg/day (25× the recommended intravaginal human dose of the suppository formulation) in rats, or 20 mg/kg/day in rabbits, or subcutaneously up to 20 mg/kg/day in rats.

Dosages at or below 10 mg/kg/day produced no embryotoxicity; however, there was a delay in fetal ossification at 10 mg/kg/day in rats. There was some evidence of embryotoxicity in rabbits and rats at 20-40 mg/kg. In rats, this was reflected as a decrease in litter size and number of viable young and reduced fetal weight. There was also delay in ossification and an increased incidence of skeletal variants.

The no-effect dose of 10 mg/kg/day resulted in a mean peak plasma level of terconazole in pregnant rats of 0.176 mcg/mL which exceeds by 17 times the mean peak plasma level (0.010 mcg/mL) seen in normal subjects after intravaginal administration of terconazole vaginal suppositories. This safety assessment does not account for possible exposure of the fetus through direct transfer to terconazole from the irritated vagina by diffusion across amniotic membranes. Since terconazole is absorbed from the human vagina, it should not be used in the first trimester of pregnancy unless the physician considers it essential to the welfare of the patient.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Animal studies have shown that rat offspring exposed via the milk of treated (40 mg/kg/orally) dams showed decreased survival during the first few post-partum days, but overall pup weight and weight gain were comparable to or greater than controls throughout lactation. Because many drugs are excreted in human milk, and because of the potential for adverse reaction in nursing infants from terconazole, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and efficacy in children have not been established.

Geriatric Use
Clinical studies of terconazole did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

ADVERSE REACTIONS
During controlled clinical studies conducted in the United States, 284 patients with vulvovaginal candidiasis were treated with terconazole vaginal suppositories 80 mg.
Based on comparative analyses with placebo (295 patients), the adverse experiences considered adverse reactions most likely related to terconazole vaginal suppositories 80 mg were headache (30.3% vs. 20.7% with placebo) and pain of the female genitalia (4.2% vs. 0.7% with placebo). Adverse reactions that were reported but were not statistically significantly different from placebo were burning (15.2% vs. 11.2% with placebo) and body pain (3.9% vs. 1.7% with placebo). Fever (2.8% v. 1.4% with placebo) and chills (1.8% vs. 0.7% with placebo) have also been reported. The therapy-related dropout rate was 3.5% and the placebo therapy-related dropout

rate was 2.7%. The adverse drug experience on terconazole most frequently causing discontinuation was burning (2.5% vs. 1.4% with placebo) and pruritus (1.8% vs. 1.4% with placebo).

OVERDOSAGE

Overdose of terconazole in humans has not been reported to date. In the rat, the oral LD 50 values were found to be 1741 and 849 mg/kg for the male and female, respectively.

The oral LD 50 values for the male and female dog were 1280 and ≥ 640 mg/kg, respectively.

DOSAGE AND ADMINISTRATION

One Zazole® Vaginal Suppository (terconazole vaginal suppositories 80 mg) should be administered intravaginally once daily at bedtime for three consecutive days.

Before prescribing another course of therapy, the diagnosis should be reconfirmed by smears and/or cultures and other pathogens commonly associated with vulvovaginitis ruled out. The therapeutic effect of terconazole vaginal suppositories is not affected by menstruation.

HOW SUPPLIED

Zazole® Vaginal Suppositories (terconazole vaginal suppositories 80 mg are available in 2.5 g, elliptically shaped white to off-white suppositories in packages of three with a vaginal applicator.

NDC 0462-0348-03

Store at 20°-25° C (68°-77° F) [see USP Controlled Room Temperature].

PharmaDerm®
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Zazole®Vaginal Suppositories (terconazole vaginal suppositories, 80 mg)

PATIENT INSTRUCTIONS

Three oval suppositories, for use inside the vagina only.

Designed to be inserted into the vagina.

HOW TO USE:

Place one suppository into the vagina each night at bedtime, for 3 nights, as directed by your doctor. The Zazole® Vaginal Suppository is self-lubricating and may be inserted with or without the applicator.

1. **Insertion with the applicator:**

1. **Filling the applicator**

- Break off suppository from the plastic strip.
- Pull the plastic completely apart at the notched end.

- Place the flat end of the suppository into the open end of the applicator as shown. You are now ready to insert the suppository into the vagina.

2. **Using the applicator:**

- Lie on your back with your knees drawn up toward your chest.
- Holding the applicator by the ribbed end of the barrel, gently insert the filled applicator into the vagina as far as it will comfortably go.
- Slowly press the plunger to release the suppository into the vagina.
- Remove the applicator from the vagina.

3. **Cleaning the applicator (Does not apply to sample applicators, which are for one time use only)**
After each use, you should thoroughly clean the applicator by following the procedure below:

- Pull the plunger out of the barrel.

- Wash both pieces with lukewarm, soapy water, and dry them thoroughly.
- Put the applicator back together by gently pushing the plunger into the barrel as far as it will go.

2. **Insertion <u>without</u> the applicator**

- Lie on your back with your knees drawn up toward your chest.
- Place the suppository on the tip of your finger as shown.
- Insert the suppository gently into the vagina as far as it will comfortably go.

NOTE: Store the suppositories at at 20°-25° C (68°-77° F) [see USP Controlled Room Temperature]. See end flap for lot number and expiration date.

A WORD ABOUT YEAST INFECTIONS

Why do yeast infections occur?

Yeast infections are caused by an organism called *Candida* (KAN di duh). It may be present in small and harmless amounts in the mouth, digestive tract, and vagina.

Sometimes the natural balance of the vagina becomes upset. This may lead to rapid growth of *Candida*, which results in a yeast infection. Symptoms of a yeast infection include itching, burning, redness, and an abnormal discharge. Your doctor can make the diagnosis of a yeast infection by evaluating your symptoms and looking at a sample of the discharge under the microscope.

How can I prevent yeast infections?

Certain factors may increase your chance of developing a yeast infection. These factors don't actually cause the problem, but they may create a situation that allows the yeast to grow rapidly.

- **Clothing:** Tight jeans, nylon underwear, pantyhose, and wet bathing suits can hold in heat and moisture (two conditions in which yeast organisms thrive). Looser pants or skirts, 100% cotton underwear, and stockings may help avoid this problem.

- **Diet:** Cutting down on sweets, milk products, and artificial sweeteners may reduce the risk of yeast infections.

- **Antibiotics:** Antibiotics work by eliminating disease-causing organisms. While they are helpful in curing other problems, antibiotics may lead to an overgrowth of Candida in the vagina.

- **Pregnancy:** Hormonal changes in the body during pregnancy encourage the growth of yeast. This is a very common time for an infection to occur. Until the baby is born, it may be hard to completely eliminate yeast infections. If you believe you are pregnant, tell your doctor.

- **Menstruation:** Sometimes monthly changes in hormone levels may lead to yeast infections.

- **Diabetes:** In addition to heat and moisture, yeast thrives on sugar. Because diabetics often have sugar in their urine, their vaginas are rich in this substance. Careful control of diabetes may help prevent yeast infections.

Controlling these factors can help eliminate yeast infections and may prevent them from coming back.

Some other helpful tips:

1. For best results, be sure to use the medication as prescribed by your doctor, even if you feel better quickly.
2. Avoid sexual intercourse, if your doctor advises you to do so. The suppository formulation may damage the diaphragm. Therefore, use of the diaphragm during therapy with the suppository is not recommended. Consult your physician.
3. If your partner has any penile itching, redness, or discomfort, he should consult his physician and mention that you are being treated for a yeast infection.
4. You can use the medication even if you are having your menstrual period. However, you should not use tampons because they may absorb the medication. Instead, use external pads or napkins until you have finished your medication. You may also wish to wear a sanitary napkin if the vaginal medication leaks.
5. Dry the genital area thoroughly after showering, bathing, or swimming. Change out of a wet bathing suit or damp exercise clothes as soon as possible. A dry environment is less likely to encourage the growth of yeast.
6. Wipe from front to rear (away from the vagina) after a bowel movement.
7. Don't douche unless your doctor specifically tells you to do so. Douching may disturb the vaginal balance.
8. Don't scratch if you can help it. Scratching can cause more irritation and spread the infection.
9. Discuss with your physician any medication you are already taking. Certain types of medication can make your vagina more susceptible to infection.
10. Eat nutritious meals to promote your general health.

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